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REVIEW ARTICLE

Guidelines for the screening and diagnosis of gestational diabetes in Italy from 2010 to 2019: critical issues and the potential for improvement

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Abstract

Aims In 2010, Italian health professionals rapidly implemented the one-step screening for gestational diabetes mellitus (GDM) based on a 75 g OGTT, to comply with the diagnostic criteria proposed by the International Association of Diabetes and Pregnancy Study Groups (IADPSG). The change was promoted by the two main Italian scientific societies of diabetology, Associazione Medici Diabetologi (AMD) and Società Italiana di Diabetologia (SID), and it took just a few months for the Istituto Superiore di Sanità, together with several scientific societies, to revise the criteria and include them in the National Guidelines System. Over the last 9 years, the implementation of these guidelines has shown some benefits and some drawbacks.

Methods In order to evaluate the critical issues arisen from the implementation of the current Italian guidelines for the diagnosis of GDM, the studies published on this topic have been reviewed. The search was performed using the following keywords: "gestational diabetes" AND "diagnostic criteria" OR screening AND Ital*. The study is an expert opinion paper, based on the relevant scientific literature published between 2010 and 2019. The databases screened for the literature review included PubMed, MEDLINE, and Scopus.

Results The implementation of the Guidelines for Screening and Diagnosis of GDM in Italy present some strengths and some weaknesses. One of the positive aspects is that high-risk women are required to perform an OGTT early in pregnancy. By contrast, there are several aspects in need of improvement: (1) In spite of the current indications, only a minority of high-risk women perform OGTT early in pregnancy; (2) several low-risk women are screened for GDM; (3) in some low-risk women affected by GDM, the diagnosis might be missed with the application of the current guidelines; (4) there is a lack of homogeneity in the risk assessment data from different regions.

Conclusions In order to improve the current Italian GDM guidelines, some practical solutions have been suggested.

Keywords Gestational diabetes · Diagnostic criteria · Maternal outcomes · Fetal outcomes · Macrosomia · Non-communicable diseases · Obesity prevention

Introduction

Gestational diabetes mellitus (GDM) is currently defined as any degree of glucose tolerance that is first recognized during pregnancy, mostly in the second or third trimester of gestation, and that is not clearly overt diabetes prior to gestation [1]. GDM, if not adequately recognized and treated, is associated with high maternal and fetal morbidity, with possible impact throughout life. In fact, women with GDM have an increased risk for developing type 2 diabetes (T2D), metabolic syndrome, and cardiovascular disease (CVD). Remarkably, the prevalence of the metabolic syndrome is three times as high in women with prior GDM compared to the control subjects [2–4]. In addition, women with prior GDM are at an increased risk for fatty liver 9–16 years postpartum [5]. For this reason, women diagnosed with GDM

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should receive lifelong screening for prediabetes, T2D, and CVD. Furthermore, children of GDM women show an increased risk of obesity, insulin resistance, and T2D over their lifetime [6–8]. Also, more than 20% of offspring born to mothers with GDM develop type 2 diabetes/prediabetes at a young age. Compared with offspring from the background population, the adjusted risks of type 2 diabetes/prediabetes are eight- and fourfold increased, respectively [9, 10]. Considering the all-encompassing impact of maternal and offspring health, a timely diagnosis and appropriate management of GDM to prevent pregnancy complications and allow for post-pregnancy interventions and follow-up must be taken into account by all stakeholders involved.

This study is an expert opinion paper, based on the relevant scientific literature published between 2010 and 2019. The research provides a summary of the "real-world" experience of implementing the IASPSG criteria [11] for diagnosis in Italy—albeit with a selective screening approach. An electronic search strategy was used to identify peer-reviewed articles evaluating the diagnostic criteria for GDM in Italy between 2010 and 2019. The search was performed using the following keywords: "gestational diabetes" AND "diagnostic criteria" OR screening AND Ital*. The databases screened for the literature review included PubMed, MEDLINE, and Scopus.

The papers were eligible if they were original studies conducted in Italy but published in English, concerning the implementation of IADPSG diagnostic criteria to detect GDM.

Studies not aimed to evaluate diagnostic criteria for GDM in Italy and/or its implementation were excluded. We also excluded letters to editors, books, books chapters, meta-analyses, reviews, and conference papers. Nine articles were identified as relevant and eligible for the final qualitative synthesis (Table 1).

Frequency of GDM

GDM is a highly prevalent complication of pregnancy, with considerable variability in different ethnic groups and screening policies. It is noteworthy that the epidemiology of GDM reflects the prevalence of impaired glucose tolerance (IGT), obesity, and T2D [12].

Several studies conducted in Italy have shown a prevalence of GDM between 3 and 10.8% [13, 14]. However, in a multicenter study conducted in Tuscany in which 2750 pregnant women underwent universal screening, the prevalence of GDM was 6.3% and that of impaired tolerance was 6.1%. Therefore, over 12% of the women studied presented some abnormalities of glucose metabolism during pregnancy [14]. The different frequency of GDM in Italian studies may be related to the timing of the screening: interestingly in some studies, the screening was performed also in the third trimester. Worldwide GDM prevalence has been reported to vary between 1 and 28%; the International Diabetes Federation (IDF) estimates that out of six live births (16.8%), one is from women affected by some form of hyperglycemia in pregnancy; the minority (16%) of these is due to diabetes in pregnancy, while the majority (84%) is related to GDM [15].

Different diagnostic criteria

"Hyperglycemia in pregnancy," defined as a "maternal hyperglycemia less severe than diabetes mellitus," is associated with increased risks of adverse pregnancy outcomes [14] and carries risks for both mothers and newborns. In this context, the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study, a large-scale multinational cohort study completed by more than 23,000 pregnant women, has shown that the risk of adverse maternal, fetal, and neonatal outcomes continuously increases as a function of maternal glycemia at 24–28 weeks of gestation, even within glucose ranges previously considered normal for pregnancy [16].

Different diagnostic criteria may lead to identifying different degrees of maternal hyperglycemia and maternal/fetal risk, prompting some experts to debate, and disagree upon, the optimal strategies for the diagnosis of GDM. Prior to the HAPO study, mainly two approaches were in use: the two-step approach (glucose challenge test with 50 g, followed if needed by a 100 g OGTT) interpreted according to the criteria proposed by O'Sullivan in 1964 and later modified by Carpenter and Coustan [17]; and the one-step approach (75 g OGTT) interpreted through the criteria suggested by WHO in 1985 [18]. Interestingly, the 100 g OGTT has been used also by the one-step approach, interpreted according to the Carpenter and Coustan criteria [17] and accepted by the National Diabetes Data Group, the American Diabetes Association (ADA), and the American College of Obstetricians and Gynecologists (ACOG), as well as in Italy.

On the basis of the results of the HAPO study, in 2010, IADPSG recommended universal screening for GDM using a one-step procedure (75 g OGTT at 24–28 weeks of gestation) and defined as diagnostic cut points for GDM a fasting plasma glucose value of 5.1 mmol/L (92 mg/dl), 1-h (10 mmol/L, 180 mg/dl), and 2-h PG (8.5 mmol/L, 153 mg/dl) during OGTT, specifying that one abnormal value is enough to diagnose GDM [19].

Although which test should be used for GDM diagnosis is still a matter of debate, mainly for the significant increase in the frequency of GDM [20], the concept of a *screening* extended to the entire population of pregnant women has been accepted by ADA, AACE, and by the Endocrine Society (ENDO). Furthermore, these criteria have been adopted by the main international scientific organizations: IDF, WHO, and, finally, the International Federation of Gynecology and Obstetrics (FIGO) [15]. In particular, in

Table 1 Studies focusing on GDM Screening and Diagnosis Italian guidelines included in the research

Study	Study design	Number of participants	Geographical location	Key outcomes
Bianchi et al. [26]	Retrospective population study	1338	Pisa, Tuscany, Central Italy	Poor application of national guidelines on screening of GDM with early screening, which is performed only in 50% of high-risk women. Diagnosis of GDM in 22% of low-risk women suggests the need to consider additional risk factors
Capula et al. [29]	Retrospective population study	2448	Catanzaro, Calabria, Southern Italy	Italian recommendations failed to identify 7.0% of women with GDM, when compared to universal screening
Pintaudi et al. [32]	Retrospective study	1015	Messina, Sicily, Southern Italy	The application of selective screening would miss 23% diagnosis of GDM in the women without risk factors. FPG value > 5.1 mmol/l and prepregnancy overweight are the two factors associated with the highest risk of developing GDM
Capula et al. [30]	Retrospective population study	3974	Catanzaro, Calabria, Southern Italy	GDM diagnosis was performed in 26% low-risk women suggesting a need for reconsidering risk stratification. Early screening was performed in only 38% of high-risk women. Capula's index has been proposed to improve accuracy of selective screening for GDM.
Corrado et al. [33]	Retrospective study	1015	Messina, Sicily, Southern Italy	The application of selective screening would miss 23% diagnosis of GDM. Prepregnancy BMI and nulliparity are predictors of GDM in women without risk factors.
Di Cianni et al. [36]	Population study	23,270	Tuscany, Central Italy	Poor application of national guidelines on screening of GDM; 40% of low-risk women being screened even if unnecessary. Among women not eligible for screening, GDM rate is relatively high (7%), supporting the need of universal screening to adequately detect all GDM cases.
Lacaria et al. [34]	Retrospective population study	2552	Tuscany, Central Italy	Poor application of national guidelines on screening of GDM with only a minority of high-risk women performing screening test early in pregnancy.

Table 1 (continued)

Study	Study design	Number of participants	Geographical location	Key outcomes
Bianchi et al. [35]	Retrospective population study	290	Pisa, Tuscany, Central Italy	Early screening was performed in 50% of high-risk women. Both groups showed similar short-term maternal–fetal outcomes. Women with early diagnosis were more frequently treated with insulin and had a better glycemic control than women with late screening;
Pintaudi et al. [45]	National survey	122 diabetes centers	Italy	Good level of reception of the current national recommendations, especially on selective screening in women at high risk for GDM; however, one-third of the diabetologists considered an FPG ≥ 92 mg/dL sufficient for the diagnosis of GDM, without the need to perform an OGTT

a comprehensive document, FIGO emphasizes the concept of "universal healthcare" for all women, addressing the problem of GDM diagnosis and treatment, and suggesting practical solutions for the management of hyperglycemia in pregnancy, even in low-income countries.

Recently, the results of the HAPO Follow-up Study, which has re-evaluated a group of about 5000 mothers enrolled during the HAPO Study [6, 7, 16] and their children 10–14 years after birth, have been published. It is noteworthy that GDM women diagnosed with the IADPSG criteria were at a high risk for glucose metabolism disorders after pregnancy; also, their children showed a high frequency of obesity as well as impaired waist circumference, due to both skinfolds and body fat percentage [2–4, 6, 7]. These data strongly suggest the adoption of IADPSG recommendations to diagnose GDM.

Italian guidelines

After the release of a national consensus paper on GDM diagnosis in 2010, the joint Diabetes and Pregnancy Study Group of AMD-SID promoted the adoption of IADPSG indications in Italy. Also, the Istituto Superiore di Sanità (ISS) acknowledged that the implementation of the new recommendations to diagnose GDM could result in a significantly higher frequency of detection of this condition. ISS therefore coordinated a panel of Italian experts in order to develop new recommendations which would take into account the results of the HAPO study and other existing scientific evidence. The document, published as national guidelines, includes most of IADPSG recommendations, as well as the position that had been taken by the most prestigious international organizations. A 75 g OGTT must be offered also when FPG is diagnostic (≥ 5.1 mmol/L, 92 mg/dl) and can help define the glycemic patterns and the appropriate approach. However, it limited the scope of the screening to women at risk of GDM rather than endorsing universal screening [21].

Although less expensive in principle, this approach has a low positive predictive value for detecting GDM and may miss up 45% of GDM cases [22]; this, however, does not seem to have significant consequences in the case of the Italian guidelines, given the fact that the risk factors on which screening is based [obesity, prior infant with macrosomia, prior GDM, first-degree relative with diabetes, age ≥ 35 years, high-risk race/ethnicity, and first-trimester FPG between 5.5 and 6.9 mmo/L (100–125 mg/dl)] are very common and, therefore, may possibly result in the enrollment of the vast majority of pregnant women. On the other hand, a selective screening approach could help focus medical resources on women with the highest risk of maternal and neonatal complications, mostly those with obesity [23–26].

Recently, the AMD-SID pregnancy study groups reviewed the recommended clinical practice for the screening and treatment of GDM, with the aim of improving the health of women and their children [27].

Critical issues with the Italian guidelines

Universal or selective screening strategy?

The selective screening approach recommended by the Italian guidelines appears not to be very sensitive,

especially among low-risk women. Some evidence has shown that 22–26% of low-risk women were screened for GDM. In addition, within this group, the prevalence of GDM is high (7–31.8%) with a wide range recorded in studies conducted in several Italian regions. These data suggest a need for reconsidering risk stratification [26, 28–30]. However, the ATLANTIC DIP, a retrospective study designed to examine predictors of GDM, showed that the prevalence of GDM among women with no risk factors ranged from 2.7 to 5.4%; significantly, women diagnosed with GDM, but without any risk factors, had worse pregnancy outcomes than women with normal glucose tolerance (NGT) [31]. These results highlight the usefulness of universal screening, emphasizing the need not to miss any GDM case, because in low-risk women with GDM, neonatal outcomes do not differ from those observed in medium- and high-risk women with GDM [31].

An Italian retrospective study, in which universal screening was adopted, showed that the prevalence of GDM in women who would be considered "low risk" according to the selective approach recommended by the Italian guidelines, amounted to 31.8%. This implies that a high number of GDM diagnoses may be missed when implementing the selective approach [29].

Similar data can be observed in a retrospective study conducted in France, which showed that selective screening was able to identify both women with a higher risk of GDM and women with more GDM-related events; however, the diagnosis of GDM was missed in almost 35% of women without risk factors [23].

A recent survey conducted throughout Sicily, in the South of Italy, suggested that selective screening based on known risk factors does not identify 23% of GDM cases [32].

This is in line with a series of studies that have shown that there is no adequate compliance to the selective screening for GDM based on risk factors, with only 50% of high-risk women being screened at 16–18 gestational weeks [26, 33–35]. Furthermore, high-risk women with a negative screening at 16–18 weeks of gestation are not tested again at 24–28 weeks, as they should be, according to the Italian guidelines. Moreover, among women not eligible for screening, the GDM rate is relatively high (7%), as well as high is the use of insulin treatment (26%), supporting the need of universal glucose screening to adequately detect all GDM cases [36]. Recent evidence showed that selective screening was not predictive of GDM among women of different ethnicity, such as India–Pakistan–Sri Lanka and Asia, supporting once more the need for universal screening, in a country like Italy, where 19.7% of 2016 newborns were offsprings of immigrant mothers [37].

Diagnosis of GDM early in pregnancy

Another significant critical point of the Italian guidelines is that they do not address how to diagnose GDM in very early pregnancy (< 16 weeks gestation), a topic which is strongly debated within the scientific societies and among experts.

Several national and international guidelines have addressed the importance of early diagnosis in pregnant women that may have previously undiagnosed T2D (overt diabetes); in fact, in recent years the age of T2D onset has progressively decreased, while the age of conception has progressively increased. In particular, first-trimester screening for preexisting DM in high-risk women through FPG, OGTT, or hemoglobin A1c has been recommended by several scientific organizations [1, 11, 15, 22] to detect preconceptional glucose metabolism abnormalities.

However, a point of debate is the appropriate cutoff value to make the diagnosis of GDM early in pregnancy. In the IADPSG guidelines, FPG values ≥ 5.1–< 6.9 mmol/L at the first prenatal visit are diagnostic of GDM. These parameters have been extrapolated from the cutoff figures used to diagnose GDM later in pregnancy. In fact, it is well known that there is a physiological drop in FPG early in normal pregnancy and that there is a strong correlation between hyperglycemia at the beginning of pregnancy—even within the range of non-diagnostic glycemic levels for diabetes—and an increased risk of adverse outcomes [38]. Indeed, evidence suggests that 60–80% of the pregnant women with FPG > 110 mg (6.10 mmol/L) early in pregnancy are quite likely to progress to GDM if there is no intervention [26, 39, 40]. Also, in the HAPO study, an FPG > 5 mmol/L (90 mg/dl) during the first trimester was associated with GDM development, increased risk of LGA offspring, and primary cesarean delivery [16].

There is evidence that the screening for GDM during the first trimester, and the subsequent treatment of hyperglycemia to a greater extent with insulin therapy in women at high risk for GDM, is associated with offsprings of appropriate gestational age, similarly to what observed in women with NGT and, as shown in a recent retrospective study conducted in Tuscany, with paradoxical lower prevalence of macrosomia, small as well as large for gestational age [36, 41]. Furthermore, early screening could prevent some diabetes-related complications in women with GDM [42].

Moreover, GDM risk factors in early pregnancy are different from those of other pregnancy periods, as shown by a recent analysis from the DALI study, which identifies a previous abnormal glucose tolerance, previous gestational diabetes mellitus, neck circumference, and resting heart rate as clinical factors independently associated with GDM and overt diabetes [43].

Therefore, evidence shows that it is important to measure FPG during the first trimester and to identify high-risk

women in order to start early intervention and possibly reduce later development of GDM and the associated adverse pregnancy outcomes [40].

On the other hand, it has been documented that there is no complete correspondence between FPG > 5.1 mmol/L (92 mg/dL) at the first trimester and the results of the OGTT performed in the third trimester, even if FPG > 5.1 mmol/L (92 mg/dL) should be considered a strong predictor of the development of GDM [40, 44].

Indeed, according to the Italian guidelines, women with FPG values between 100 and 125 mg/dl (5.6–6.9 mmol/L) early in pregnancy are considered at high risk of GDM, so they must be screened at the 16th gestational week. A national survey promoted in 2013 by the Italian Diabetes in Pregnancy Study Group showed there is a good level of reception of the current national recommendations, documenting that most diabetologists applied selective screening and 84% prescribed OGTT at 16–18 weeks of gestation in women at high risk for GDM; however, one-third of the diabetologists considered an FPG ≥ 5.1 mmol/L (92 mg/dL) sufficient for the diagnosis of GDM, without the need to perform an OGTT [45].

Heterogeneity of GDM

Recent studies have shown that some unconventional risk factors, such as the assisted reproductive technology (ART), are strong predictors of the development of GDM [46, 47]. Although obesity and overweight are known as the major risk factors for GDM, several studies have reported that genetic and autoimmune features add to this risk. Indeed, 10% of women with GDM have specific autoantibody against beta cells and fewer features of insulin resistance, requiring more often insulin therapy during pregnancy than women without autoantibodies [48]. These women may develop type 1 diabetes during or after pregnancy, or they may develop latent autoimmune diabetes of adulthood (LADA), often several years after pregnancy. For this reason, GDM-affected women presenting autoimmune features, such as young age, a low BMI, an early diagnosis of GDM, and an early need for insulin therapy to control hyperglycemia, should be screened for specific beta cell autoimmunity during and after pregnancy, so as to avoid maternal and fetal complications of type 1 diabetes during pregnancy, or its acute onset at a later time [49]. Moreover, many studies reported a high prevalence of GDM in non-obese women without autoimmune features, suggesting that GDM is a heterogeneous disease with a genotypic and phenotypic diversity that also includes patients progressing toward LADA or type 1 diabetes, as well as patients affected by MODY [50, 51]. The diagnosis of MODY in pregnancy is essential, due to the fact that the management of this condition is different from the management of other forms of GDM. MODY is a rare familiar form of autosomal dominant diabetes by genetic mutations resulting in β-cells dysfunction. At least thirteen subtypes of MODY have been identified, featuring different phenotypes and ages of onset; the prevalence of MODY amounts to roughly 1–2% of patients with diabetes, probably underestimated. In GDM the prevalence of MODY can be up to 6% [52–55].

Such evidence suggests the need for universal screening, which could identify GDM in women who are not presenting features of insulin resistance.

Universal versus selective screening: healthcare cost

In the debate on universal screening, a major problem is represented by healthcare costs. With the adoption of universal screening, the anticipated increase in the incidence of GDM would have a substantial impact on healthcare costs.

A cost analysis of GDM screening strategies was conducted in the USA to determine whether adopting the IADPSG criteria would be cost-effective, compared with the current standard of care. The research compared three strategies to identify GDM: (1) no screening; (2) current screening practice (1-h 50-g glucose challenge test between 24 and 28 weeks followed by 3-h 100-g glucose tolerance test when indicated); or (3) screening practice proposed by IADPSG. The results showed that although there are potential perinatal advantages associated with the IADPSG guidelines, they do not outweigh the costs related to the increase in the number of detected GDM cases. This analysis proves that the IADPSG approach to GDM screening and diagnosis is cost-effective compared with selective screening, when a GDM diagnosis provides an opportunity for early and intensive intervention and prevention [56].

Universal screening could therefore increase the costs initially, because the patients at risk will require more visits for their lifestyle changes and frequent screening to monitor their progression to diabetes; however, by identifying these patients, there will be long-term cost savings. Several studies, including those of the Diabetes Prevention Program Research Group, have shown that intense lifestyle modification can effectively reduce the incidence of future diabetes by as much as 50% in women previously diagnosed with GDM [57].

However, selective screening will inevitably miss women with GDM, and women with undiagnosed GDM will have both maternal and fetal complications.

Conclusions and recommendations

In Italy, the implementation of the current Guidelines for Screening and Diagnosis of Gestational Diabetes presents some critical issues: (1) Unfortunately, in spite of the current

indications, just a minority of high-risk women perform OGTT early in pregnancy; (2) low-risk women are screened for GDM, in contrast to the current guidelines; (3) the implementation of the current guidelines misses out on the diagnosis of some GDM-affected women, who are considered at low risk; (4) there is a lack of homogeneity in the risk assessment data from different regions.

How can we address these issues?

High-risk women. In agreement with the current guidelines, we highlight the need for high-risk women to perform an OGTT early in pregnancy (between 16 and 18 gestational weeks); if the results are within range, they should be re-evaluated between 24 and 28 gestational weeks.

Fasting plasma glucose. It is known that there is a strong correlation between early pregnancy hyperglycemia and an increased risk of adverse outcomes, even within the range of glucose levels non-diagnostic for diabetes. Therefore, patients with FPG values between 5.1 and 6.9 mmol/L (100 and 125 mg/dl) early in pregnancy should undergo OGTT at the 16th gestational week. Studies are warranted to verify the possible impact of proper counseling (diet and physical activity) in terms of reduction in the frequency of GDM in these women.

Universal screening, as shown by several studies, could enable us to make a diagnosis also in low-risk women that can develop GDM and also detect patients showing unconventional risk factors, such as ART. This universal screening, which would include OGTT at 24–28 weeks of gestation in all pregnant women, will enable to detect all GDM cases, including autoimmune GDM, which characterizes women at high risk of progression toward LADA or type 1 diabetes.

"Awareness campaigns" targeted to the general population are needed. In addition, all stakeholders involved (Ministry of Health, scientific societies, diabetologists, general practitioners, obstetricians) should coordinate to perform specific tasks, according to their specific mission [58].

Author contributions EV researched data, contributed to discussion and wrote the manuscript. ES researched data and wrote the manuscript. AL reviewed the manuscript and contributed to the discussion. MS reviewed and edited the manuscript. GS, MB, DM, FP, GDC, ET, AN, CL, AT, CF, and ADB have reviewed critically the manuscript. All authors were involved in critical revision and approved the final version of the manuscript before submission.

Compliance with ethical standards

Conflict of interest No potential conflicts of interest relevant to this article were reported.

Statement of human and animal rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study, formal consent is not required.

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